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MARVIN J SPIVAK  
OBLON SPIVAK MCCLELLAND MAIER & NEUSTADT  
FOURTH FLOOR  
1755 JEFFERSON DAVIS HIGHWAY  
ARLINGTON, VA 22202

EXAMINER

STEADMAN, DAVID J

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 06/18/2002

18

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/459,573

Applicant(s)

LIVSHITS ET AL.

Examiner

David J. Steadman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-44 is/are pending in the application.
- 4a) Of the above claim(s) 1(C)-(H), 4-6, 8-10, and 14-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 7, 11-13 and 27-44 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____.  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____. | 6) <input type="checkbox"/> Other:  |

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## **DETAILED ACTION**

### ***Status of the Application***

Claims 1-44 are pending in the application.

Amendment to the specification and claim 1 and addition of claims 27-44 in Paper No. 16, filed 04/08/02 is acknowledged.

It is noted that while claims 1 (C)-(H), 4-6, 8-10, and 14-26 were withdrawn from consideration in the Office action of Paper No. 14, the restriction requirement was not made final. Therefore, in order to clarify the record, the restriction requirement as set forth in Paper No. 11 is still deemed proper and is therefore made FINAL.

Claims 1 (C)-(H), 4-6, 8-10, and 14-26 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Applicants' arguments filed in Paper No. 16 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

### ***Claim Objections***

1. Claims 1-3 and 7 are objected to as reciting non-elected subject matter of parts (C)-(H) of claim 1. It is suggested that applicants remove the non-elected subject matter.

### ***Claim Rejections - 35 USC § 101***

2. The rejection of claims 1-3, 7, 11, and 27-44 under 35 U.S.C. 101 is maintained. The rejection was fully explained in a previous Office action.

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Applicants argue that by amending claim 1 to recite "which has been modified to increase", the claim clearly indicates a non-natural microorganism. Applicants' argument has been fully considered but is not found persuasive to overcome the rejection. Modifications, particularly to prokaryotic organisms in response to environmental stress, frequently occur in nature. As such it is unclear from the claims as to whether the modification is a natural modification or is a modification due to the hand of the inventor. It is suggested that applicants insert the term "purified" or "isolated" in claim 1 to differentiate the bacteria of claims 1-3, 7, 11, and 27-44 from those found in nature.

***Claim Rejections - 35 USC § 112, Second Paragraph***

3. Claims 1-3, 7, 11-13, and 27-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. The rejection of claims 1 (claims 2, 3, 7, and 27-44 dependent therefrom) and 11 (claims 12 and 13 dependent therefrom) as being unclear in the recitation of the term "increased" is maintained. Applicants argue the a skilled artisan would recognize the expression amount is increased relative to that of the unmodified bacterium. Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

The claims remain unclear as to what the increased level of expression is being compared. A skilled artisan would not necessarily recognize that the expression level of the modified bacterium is being compared to an unmodified bacterium, i.e., a wild-type bacterium, as one of skill in the art would recognize the expression level of the modified bacterium could be compared to another modified bacterium. It is suggested that applicants identify to what the expression amount is being compared.

5. Claims 36-44 are confusing in the recitation of "The method of Claim 1" as claim 1 is drawn to a bacterium and not a method. It is suggested that applicants clarify the meaning of the claims.

***Claim Rejections - 35 USC § 112, First Paragraph***

6. The scope of enablement rejection of claims 1-3, 7, 11-13, and 27-35 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action. Applicants traverse the rejection arguing that based on the teachings of the instant specification, a skilled artisan would recognize methods for increasing copy number thereof or increasing expression of the encoded protein. Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

It is noted that claim 1 (claims 2, 3, 7, and 27-44 dependent therefrom) is not limited to a modified bacterium with increased polypeptide expression by increasing a nucleic acid copy number. Instead, claim 1 is drawn to an Escherichia bacterium that has been modified by *any* method to increase polypeptide expression. However, the specification provides only a single method of increasing bacterial expression of the recited polypeptides, i.e., by transformation of an Escherichia bacterium with an expression vector for overexpression of the nucleic acid of SEQ ID NO:9 encoding the polypeptide of SEQ ID NO:10. Furthermore, the scope of proteins recited in claim 1 part (B), i.e., "a protein... which has an activity of increasing the ability to produce the L-amino acid", is not enabled by the instant specification. The specification is *not* enabling for *any* protein that is encoded by a nucleic acid that hybridizes to SEQ ID NO:9 having *any* activity to increase amino acid production of the bacterium expressing the protein. The activity of the disclosed polypeptides is the export of amino acids. The disclosed polypeptides do not exhibit *any* activity that results in increased amino acid production of a bacterium expressing the disclosed polypeptides. Therefore, the scope of claimed bacteria is not commensurate in scope with the enablement provided in the specification.

Applicants argue that glutamate, lysine, and proline have different properties and therefore, because the specification discloses increased E. coli production of these amino acids by overexpression of the polypeptide of SEQ ID NO:10, one of skill in the art would reasonably expect that an E. coli

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overexpressing the polypeptide of SEQ ID NO:10 would similarly have increased yields of *all* amino acids.

Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

The specification actually discloses that overexpression of the yahn gene, i.e., SEQ ID NO:9 encoding the polypeptide of SEQ ID NO:10, does *not* increase yields of *any* amino acid. The specification discloses "[e]xcept for the Yahn, every of the presumed transporters have specificity to several substrates" (page 25, lines 5 and 6), thereby suggesting that the YAHN polypeptide is specific for particular amino acids and not all amino acids. The instant specification demonstrates increased levels of proline when the yahn gene is overexpressed in E. coli strains TG1 and VL2151 (pages 25 and 35), increased yields of glutamate when overexpressed in E. coli strain AJ13199 (page 27), and increased yields of lysine when overexpressed in E. coli strain W3110(tyrA) transformed with plasmid pCABD2 (page 28). The instant specification does not demonstrate increased yields of any other amino acids besides proline, lysine, and glutamate. Therefore, based on applicants' disclosure, one of skill in the art would recognize the YAHN transporter polypeptide of SEQ ID NO:10 is specific *only* for proline, lysine, and glutamate when expressed in particular strains of E. coli. Applicants have provided guidance and working examples demonstrating increased production of *only* proline, lysine, and glutamate and it is highly unpredictable as to whether overexpression of the polypeptide of SEQ ID NO:10 will increase yields of *all* amino acids. Therefore, the specification does not enable the entire scope of the claimed invention.

### ***Claim Rejections - 35 USC § 103***

7. The rejection of claims 1, 2, 11-13, and 27 under 35 U.S.C. 103(a) as being unpatentable over Blattner et al. (GenBank Accession Number P75693, 01 November 1997) in view of Vrljic et al. (Mol Microbiol 22:815-826), and US Patent 6,040,160 is maintained. The rejection was fully explained in a previous Office action.

Applicants traverse the rejection by arguing that the disclosure of Blattner et al. teaches the YAHN polypeptide belongs to the LysE protein family, which Blattner discloses is based on Pfam accession

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number PF01810. Applicants argue Pfam accession number PF01810 is based on the reference of Aleshin et al. (Trends Biochem Sci 24:133-135, published April 1999), which was published after the filing date of the instant application. Applicants have provided a copy of Pfam accession number PF01810 and an abstract of Aleshin et al. in support of their argument. Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

It is noted that applicants have correctly interpreted the examiner's position that the YAHN polypeptide belongs to the LysE protein family. The examiner has based his position on the teaching of Blattner et al. It is further noted that the listing under the heading "LysE type translocator" of Pfam accession number PF01810 appears to be based solely on the reference of Vrljic et al. ("[1]" of Pfam accession number PF01810) as cited in the instant rejection and not Aleshin et al. This listing, as based on the reference of Vrljic et al., clearly identifies LysE as a lysine export polypeptide and suggests the use of the polypeptide in the industrial production of L-lysine. This listing clearly supports the teachings of Vrljic et al. as described in a previous Office action. While Pfam accession number PF01810 cites Aleshin et al. ("[2]" of Pfam accession number PF01810), the reference of Aleshin et al. does not appear to be relied upon in the listing or description of LysE. Therefore, based on the combined teachings of Blattner et al., Vrljic et al. and US Patent 6,040,160, claims 1, 2, 11-13, and 27 would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

### ***Conclusion***

8. No claim is in condition for allowance. All claims are rejected.

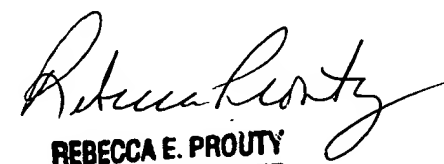
Applicant's addition of claims 36-44 necessitated the new ground(s) of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

  
**REBECCA E. PROUTY**  
**PRIMARY EXAMINER**  
**GROUP 1600**  
1600